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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

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*Ex parte* DALE B. SCHENK

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Appeal 2010-004495
Application 10/777,792
Technology Center 1600

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Before ERIC GRIMES, JEFFREY N. FREDMAN, and
STEPHEN WALSH, *Administrative Patent Judges*.

WALSH, *Administrative Patent Judge*.

DECISION ON APPEAL[1]

This is an appeal under 35 U.S.C. § 134(a) involving claims to a composition comprising a beta-amyloid peptide, Aβ1-7, linked to a toxoid from a pathogenic bacterium to form a conjugate. The Patent Examiner

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[1] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, or for filing a request for rehearing, as recited in 37 C.F.R. § 41.52, begins to run from the "MAIL DATE" (paper delivery mode) or the "NOTIFICATION DATE" (electronic delivery mode) shown on the PTOL-90A cover letter attached to this decision.

rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

## STATEMENT OF THE CASE

The invention concerns a composition comprising an Aβ1-7 peptide linked to a toxoid from a pathogenic bacterium to form a conjugate. The Specification states that "Aβ, also known as β-amyloid peptide ... is a peptide of 39-43 amino acids, which is the principal component of characteristic plaques of Alzheimer's disease." (Spec. 15, [0071]). The Specification also explains that Aβ generates "an immune response in excess of that of other antigens." (*Id.*, [0072]). According to the Specification, preferred immunogenic fragments for linking to a toxoid "include Aβ1-5, 1-6, 1-7, 1-10, 3-7, 1-3, and 1-4." (*Id.* at 16, [0077]). Some compositions of the invention also comprise an adjuvant that "augment[s] the intrinsic response to an immunogen without causing conformational changes in the immunogen that affect the qualitative form of the response." (*Id.* at 40, [0156]). QS-21 is said to be a preferred adjuvant. (*Id.* at 41, [0157]).

Claims 119-143 are on appeal. Claims 119, 131 and 133 are representative and read as follows:

119. A composition comprising an Aβ peptide linked to a carrier which is a toxoid from a pathogenic bacterium to form a conjugate, wherein the Aβ peptide is Aβ1-7.

131. A composition comprising (a) an Aβ peptide linked to a carrier which is a toxoid from a pathogenic bacterium to form a conjugate, wherein the Aβ peptide is Aβ1-7 and (b) an adjuvant.

133. The composition of claim 131, wherein the adjuvant comprises QS-21.

The Examiner rejected the claims as follows:

• claims 119, 121-125, and 131 under 35 U.S.C. § 103(a) as unpatentable over Selkoe,[2] Wong,[3] and Penney;[4]

• claims 119-125 and 131-132 under 35 U.S.C. § 103(a) as unpatentable over Selkoe, Wong, Penney, and Restifo;[5]

• claims 119, 121-125, 131 and 133-138 under 35 U.S.C. § 103(a) as unpatentable over Selkoe, Wong, Penney, and Hancock;[6] and

• claims 119, 121-131 and 133-143 under 35 U.S.C. § 103(a) as unpatentable over Selkoe, Wong, Penney, Hancock, and Collier.[7]

Claims 120-132 and 139-143 have not been argued separately and therefore stand or fall with claim 119; claims 134-138 stand or fall with claim 133. 37 C.F.R. § 41.37(c)(1)(vii).

## OBVIOUSNESS

*The Issue*

The Examiner's position is that Wong disclosed a conjugate for producing antibodies against Aβ, comprising Aβ1-10 linked to KLH, a carrier protein and antigen that increases the immune system reaction to the

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[2] US Patent No. 5,262,332 issued to Dennis J. Selkoe, Nov. 16, 1993.
[3] Caine W. Wong et al., *Neuritic plaques and cerebrovascular amyloid in Alzheimer disese are antigenically related*, 40 PROC. NATL. ACAD. SCI. 8729-8732 (1985).
[4] US Patent No. 5,773,007 issued to Christopher L. Penney et al., Jun. 30, 1998.
[5] US Patent No. 5,733,548 issued to Nicholas P. Restifo et al., Mar. 31, 1998.
[6] US Patent No. 5,723,130 issued to Gerald E. Hancock et al., Mar. 3, 1998.
[7] US Patent No. 5,601,827 issued to R. John Collier et al., Feb. 11, 1997.

molecule with which it is conjugated. (Ans. 3-4). The Examiner found that Wong taught that antibodies raised against the conjugate are useful for detecting Aβ and diagnosing Alzheimer's disease. (*Id.* at 4).

The Examiner found that Selkoe also disclosed a method of detecting and diagnosing Alzheimer's disease using antibodies to Aβ. (*Id.* at 3). The Examiner found that Selkoe taught a method of making the antibodies by using fragments of about 8 or more amino acid residues of β-AP. (*Id.*). According to the Examiner, Selkoe's "about 8" includes 7 amino acids, as recited in instant claim 119. (*Id.*). Turning to Penney, the Examiner found that this reference taught that purified antigens (protein-conjugates) are not optimally effective in eliciting an antibody response. (*Id.* at 4). However, the Examiner found that Penney disclosed that if an immunostimulant such as the diphtheria toxoid CRM 197 or KLH carrier molecule is included in the composition, the antibody response will be boosted. (*Id.*).

According to the Examiner, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to make a composition comprising Aβ1-7 covalently linked to CRM 197. The Examiner reasoned that because Wong disclosed coupling residues 1-10 of Aβ, i.e., Aβ1-10, to a heterologous protein to increase antigenicity, it would have been obvious to select a shorter peptide for this purpose. In particular, the Examiner reasoned that Selkoe suggested using 7 amino acids of Aβ by disclosing the use "of about 8" amino acids of Aβ. (*Id.* at 3, 4). The Examiner also reasoned that because Penney taught that CRM 197 and KLH are both effective carriers that increase antigenicity, it would have been obvious to simply substitute the toxoid CRM 197 for Wong's KLH. (*Id.* at 4).

Regarding claim 133, the Examiner found that Penney taught that adjuvants can optionally be added to antibody-inducing compositions to mitigate local hypersensitivity to the carrier or to increase immunogenicity. (*Id.* at 4, 5). Additionally, the Examiner found that Hancock taught that "QS-21 … is particularly suitable as an adjuvant as it increases the immune response, resulting in more antibodies that tightly bind to the antigen administered." (*Id.* at 5-6). According to the Examiner, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to select QS-21 as an adjuvant to be included with the conjugate suggested by Selkoe, Wong and Penney because Hancock taught that QS-21 was known to be particularly effective in eliciting antibodies. (*Id.* at 6).

Appellant contends that the Examiner has not established a prima facie case of obviousness, alleging that the prior art "provided no or insufficient reason for the artisan to have used a fragment of Aβ of only seven amino acids [nor] any reason that these seven amino acids should correspond to Aβ1-7…." (Reply Br. 4). Appellant also asserts that the "purported switch from a preferred carrier for use in animals to a carrier suitable for use in humans without any proposal of human use represents hindsight ….." (*Id.*). Additionally, Appellant asserts that it would not have been obvious to include Hancock's QS-21 adjuvant in the combination. Further, Appellant contends that "the claimed conjugate is an unexpectedly superior agent for human therapeutic administration" and "unexpectedly advantageous for therapeutic use" relative to Wong's conjugate. (*Id.*).

The issues with respect to this rejection are:

whether it would have been obvious to a person of ordinary skill in the art at the time the invention was made to combine the teachings of Wong and Selkoe to make a conjugate comprising an Aβ1-7 fragment;

whether modifying the conjugate of Wong and Selkoe by exchanging Wong's KLH carrier protein for Penney's CRM 197 carrier protein amounted to a simple, predictable substitution of one known element for another;

whether it would have been obvious to a person of ordinary skill in the art at the time the invention was made to select QS-21 as the adjuvant for the modified conjugate composition of Wong, Selkoe and Penney; and

whether Appellant has established that the claimed invention provided unexpected results sufficient to rebut a prima facie case of obviousness.

*Findings of Fact*

1. We adopt the Examiner's findings of facts. (*See* Ans. 3-7).

2. Selkoe stated that "smaller β-AP fragments of 8 or more amino acids[] can be used as an immunogen to produce peptide antibodies that can be used to detect β-AP deposits in [Alzheimer's Disease] patients." (Selkoe col. 21, ll. 18-23).

*Principles of Law*

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007). "If a person of

ordinary skill can implement a predictable variation, § 103 likely bars its patentability." *Id.* at 417.

A showing of unexpected results must be commensurate in scope with the breadth of the claims. *In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983).

*Analysis*

*A. The Rejection over Selkoe, Wong and Penney*

The Examiner correctly found (Ans. 3-4) that Selkoe taught using a fragment of about 8 amino acid residues of Aβ, which we agree includes a fragment of 7 amino acid residues, to produce antibodies to Aβ. Similarly, Wong disclosed using an Aβ fragment to produce antibodies to Aβ. Wong's peptide comprised the first 10 residues of Aβ and coupled the fragment to a carrier protein to form a conjugate.

These combined disclosures would have suggested to a person of ordinary skill in the art at the time the invention was made that Wong's peptide may be effectively synthesized using fewer than the first 10 residues of Aβ, i.e., the first 7 residues of Aβ. The fact that Wong did not expressly disclose an advantage "in clearing Aβ deposits" as asserted by Appellant (App. Br. 11) does not establish that the Examiner's combination was impermissibly based upon hindsight. We conclude that the combination of the known elements of Wong and Selkoe in a known manner amounted to a predictable variation that could have been implemented by a person of ordinary skill. *KSR*, 550 U.S. at 416.

Nor are we persuaded by Appellant's assertion that an artisan would not have had a reason to use select an antibody that binds within residues 1-

10 of Aβ (Wong's peptide) instead of the "numerous other antibodies to Aβ [that were] subsequently described in the art for diagnosis," such as C-terminal antibodies. (App. Br. 11). This argument only suggests that compositions comprising additional Aβ fragments may also have been obvious at the time of the invention, but not that the claimed composition was nonobvious over the combination of the cited prior art.

Appellant's assertion that Selkoe "would have discouraged the use of small synthetic fragments of Aβ for generating antibodies for purposes of diagnosis" (App. Br. 11) is not supported by the evidence. As the Examiner explained (Ans. 9), Selkoe specifically taught that synthetic Aβ fragments of about 8 or more amino acids were immunogens to produce antibodies that could be used to detect Aβ deposits in Alzheimer's Disease patients. (*See* FF-2). Nor do we find that Selkoe's teaching to use a fragment of about 8 or more residues suggested "that a fragment of 8 residues is about the minimum size and that if a smaller fragment is used there is at least a risk of failure," as asserted by Appellant (App. Br. 12). We agreed above with the Examiner that Selkoe's teaching "of about 8" residues is correctly interpreted to include the use of a fragment having 7 residues; to interpret it otherwise would render "about" superfluous.

We are also unpersuaded by Appellant's assertion that it would not have been obvious to substitute Wong's KLH carrier with CRM 197. (App. Br. 10). Penney's disclosure of KLH as a preferred carrier for animal use was consistent with the broader teaching that both KLH and CRM 197 were effective carrier molecules. (*See* Ans. 4). Thus, the Examiner's proposed modification merely requires "the simple substitution of one known element for another" *see KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 417 (2007),

and is not the result of impermissible hindsight reconstruction, as Appellant contends (*see* App. Br. 10).

Appellant further asserts that "[p]atentability is further evidenced by two unexpected results of the claimed conjugate vis-à-vis the cited art." (App. Br. 12). Appellant asserts that the claimed conjugates are unexpectedly superior to Wong's conjugates for human therapeutic use, as shown by "Table 16 . . .(p. 99)," said to show that "antibodies binding to an epitope within residues 1-7 of Aβ are particularly advantageous." (*Id.* at 11.) Table 16, entitled "Analysis of Epitope Specificity" appears at page 98. According to Table 16, N-term mab 3D6 recognized epitope 1-5, mab 10D5 recognized epitope 3-6, and mab 22C8 recognized epitope 3-7. Appellant has not pointed us to evidence that a conjugate of toxoid and Aβ1-7 was used as the antigen to generate those antibodies. In our independent review of the Specification, we have not found evidence that a toxoid conjugate of Aβ1-7 was used to generate the data in Table 16. It appears, for example that mab 10D5 was generated by using a conjugate of sheep-anti-mouse IgG with Aβ1-12, not a claimed conjugate. (See Spec. 65-71, ¶¶ [0267], [0282], [0285], and Tables 5 and 6.)

As Appellant referred to Table 16 as being on page 99, we have also reviewed the table appearing on page 99, i.e, Table 17. Table 17 likewise does not state that a conjugate of Aβ1-7 was used to generate any of the antibodies whose properties are shown. Because Appellant did not provide evidence that a claimed toxoid conjugate of Aβ1-7 was used to generate the data said to show unexpected results, we agree with the Examiner that "Appellant is arguing about the advantages of different products from those

claimed." (Ans. 8.) Such evidence is insufficient to overcome prima facie obviousness. *See Grasselli*, 713 F.2d at 743.

*B. The Rejection Over Selkoe, Wong, Penney and Restifo*

Appellant contends that claims 119-125 and 131-132 would not have been obvious over the combination of Selkoe, Wong, Penney and Restifo for the same reasons argued with respect to the combination of Selkoe, Wong, and Penney. (App. Br. 15). We are unpersuaded of Examiner error for the reasons discussed in part A.

*C. The Rejection Over Selkoe, Wong, Penney and Hancock*

To the extent Appellant contends that claims 119, 121-125, 131 and 133-138 would not have been obvious over the combination of Selkoe, Wong, Penney and Hancock for the same reasons argued with respect to the combination of Selkoe, Wong, and Penney (App. Br. 15), we remain unpersuaded for the reasons discussed in part A.

Regarding claims 133-138, Appellant additionally asserts that "Hancock would not have motivated replacement of Freund's adjuvant by Wong in favor of QS-21." (*Id.* at 15). According to Appellant, "QS-21 is not indicated to improve or even be equally effective for stimulation of antibodies relative to Freund's adjuvant ... [which is] restricted to animal use." (*Id.* at 15-16). We agree with the Examiner's finding and explanation that, while differences exist between QS-21 and Freund's adjuvant, both were known in the art at the time of the invention to be effective adjuvants for increasing immune response. (Ans. 11-12.) The Examiner's combination involved "the simple substitution of one known element for another." *See KSR Int'l Co.*, 550 U.S. at 417.

Appellant's assertion that this substitution "confers an unexpected benefit for use in humans ... because Aβ1-7 was not known to have any therapeutic use in humans, as discussed previously" (App. Br. 16) is misdirected and insufficient to overcome prima facie obviousness for the reasons already discussed.

*D. The Rejection Over Selkoe, Wong, Penney, Hancock, and Collier*

Appellant contends that claims 119, 121-131 and 133-143 are not obvious over the combination of Selkoe, Wong, Penney, Hancock and Collier for the same reasons set forth above with respect to the combination of Selkoe, Wong, Penney and Hancock. (App. Br. 17). Consequently, we are unpersuaded for the reasons discussed in part C.

## CONCLUSIONS OF LAW

The evidence supports the Examiner's conclusion that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to combine the teachings of Wong and Selkoe to make a conjugate comprising an Aβ1-7 fragment.

Modifying the conjugate of Wong and Selkoe by exchanging Wong's KLH carrier protein for Penney's CRM 197 carrier protein would have been a simple and predictable substitution of one known element for another.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to select QS-21 as the adjuvant for the modified conjugate composition of Wong, Selkoe and Penney.

Appellant has not established that the claimed invention provided unexpected results sufficient to rebut the prima facie case of obviousness.

SUMMARY

We affirm the rejection of claims 119, 121-125, and 131 under 35 U.S.C. § 103(a) over Selkoe, Wong, and Penney;

we affirm the rejection claims 119-125 and 131-132 under 35 U.S.C. § 103(a) over Selkoe, Wong, Penney, and Restifo;

we affirm the rejection of claims 119, 121-125, 131 and 133-138 under 35 U.S.C. § 103(a) over Selkoe, Wong, Penney, and Hancock; and

we affirm the rejection of claims 119, 121-131 and 133-143 under 35 U.S.C. § 103(a) over Selkoe, Wong, Penney, Hancock, and Collier.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

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